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## **Chronisch venöse Insuffizienz bei postthrombotischem Syndrom und Varikose**

Hafner, J ; Mayer, D ; Amann, B ; French, L E ; Läuchli, S ; Hofer, T ; Ramelet, A A ; Jeanneret, C

**Abstract:** Venous disorders have a high prevalence and require approximately 1% of health budgets of industrialized countries. The postthrombotic syndrome (PTS) is defined by subjective symptoms and morphologic trophical skin changes following deep venous thrombosis. Prevention of venous thromboembolism in risk situations, easy availability of diagnostic tools (D-dimers, colour-coded duplex sonography) and early detection of deep venous thrombosis, as well as immediate therapeutic anticoagulation along with leg compression during the acute phase and over a two year period of time significantly reduce the incidence of PTS. Chronic venous insufficiency (CVI) includes trophical skin and soft tissue pathologies of the lower leg due to venous hypertension in the distal venous system of the lower extremity. Roughly, two main causes can be distinguished. (A) Deep venous insufficiency (A1 in postthrombotic syndrome; A2 in primary deep venous insufficiency) and (B) superficial venous reflux, usually varicose veins. Compression therapy, surgical ablation of superficial venous reflux, and tangential ablation with split skin graft (shave treatment) of refractory venous ulcers are the mainstays in the treatment of CVI.

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Other titles: Chronic venous insufficiency in postthrombotic syndrome and varicose veins

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# Martorell Hypertensive Ischemic Leg Ulcer

## A Model of Ischemic Subcutaneous Arteriolosclerosis

Jürg Hafner, MD; Stephan Nobbe, MD; Hugo Partsch, MD; Severin Läuchli, MD; Dieter Mayer, MD; Beatrice Amann-Vesti, MD; Ruedi Speich, MD; Christoph Schmid, MD; Günter Burg, MD; Lars E. French, MD

**Objectives:** To better define the diagnosis and treatment of Martorell hypertensive ischemic leg ulcer (HYTILU) and to compare Martorell HYTILU with calciphylaxis (calcific uremic arteriopathy) and non-uremic forms of calciphylaxis.

**Design:** Retrospective study from 1999 through 2007.

**Setting:** Department of Dermatology, University Hospital of Zurich, Zurich, Switzerland.

**Participants:** Of 330 patients with leg ulcers, 31 had a clinical diagnosis of Martorell HYTILU confirmed by dermatopathologic examination.

**Main Outcome Measures:** Clinical features, suspected diagnosis at initial presentation, cardiovascular risk factors, findings from vascular examination and histologic analysis, specific medical and surgical management, and outcome.

**Results:** Of the 31 patients, all presented with 1 or multiple painful necrotic skin ulcers on the laterodorsal part

of the leg, with bilateral involvement in 16 of 31 cases (52%), and 16 were referred with suspected pyoderma gangrenosum. All patients had arterial hypertension, and 18 (58%) had diabetes. All patients had subcutaneous stenotic arteriolosclerosis on histologic analysis, with medial calcification in 22 of 31 of cases (71%). Martorell HYTILU, calciphylaxis, and nonuremic forms of calciphylaxis shared identical histologic features. Of the 31 patients, 29 (94%) were successfully treated with surgical debridement and split-thickness skin grafting. Three patients (9%) died of sepsis, 2 of whom were undergoing immunosuppressive treatment for wrongly diagnosed pyoderma gangrenosum.

**Conclusions:** Ischemic subcutaneous arteriolosclerosis is the hallmark of Martorell HYTILU, calciphylaxis, and the nonuremic forms of calciphylaxis. All patients are hypertensive and approximately 60% are diabetic. Martorell HYTILU can easily be confused with pyoderma gangrenosum, which can be detrimental, since the 2 diseases require a completely different treatment strategy.

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**Author Affiliations:** Departments of Dermatology (Drs Hafner, Nobbe, Läuchli, Burg, and French), Cardiovascular Surgery (Dr Mayer), and Internal Medicine (Drs Amann-Vesti, Speich, and Schmid), University Hospital of Zurich, Zurich, Switzerland; and Department of Dermatology, Wilhelminen Hospital, Vienna, Austria (Dr Partsch [retired]).

**M**ARTORELL HYPERTENSIVE ischemic leg ulcer (HYTILU) was originally described by Fernandes Martorell in 1945 in Barcelona, Spain.<sup>1</sup> Martorell described 4 obese, hypertensive female patients with painful leg ulcers on the lateral aspect of their legs. One year later, Hines and Farber and coworkers<sup>2,3</sup> reported an association of such leg ulcers with the histologic presence of hypertrophic stenotic subcutaneous arterioles and coined the term *hypertensive-ischemic ulcer*. In 1966, Schnier et al<sup>4</sup> reported a series of 40 patients with HYTILU, pointing out the very characteristic location of the principal lesion on the laterodorsal lower leg. In 1995, Lazareth and Priollet<sup>5</sup> described the benefit of skin grafting for the treatment of *l'angiodermite nécrotique*, the term used by the French to describe HYTILU, which was confirmed by Henderson et al<sup>6</sup> in a survey on 16 patients. The literature on HYTILU is otherwise scarce,<sup>7</sup> and to our knowledge, studies ana-

lyzing the clinical and dermatopathologic characteristics and possible therapies on a significant number of patients do not exist.

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At our department, Martorell HYTILU has become one of the leading causes of chronic leg ulceration in the past 10 years. Martorell HYTILU shares striking clinical and histopathological similarities with calciphylaxis (calcific uremic arteriopathy)<sup>8-11</sup> and eutrophication in morbid obesity.<sup>12</sup> The latter has recently been referred to as "calciphylaxis with normal renal and parathyroid function"<sup>13</sup> or "calciphylaxis from non-uremic causes."<sup>14</sup> This study of a large series of patients with Martorell HYTILU defines common pathophysiologic hallmarks of 4 entities that are linked to ischemic subcutaneous arteriolosclerosis (**Table 1**) and outlines treatment protocols.

**Table 1. Four Manifestations of Ischemic Arteriosclerosis**

Disease	Distal	Proximal
ESRD	Calciphylaxis, distal pattern <i>Synonym:</i> calcific uremic arteriopathy <i>Distal:</i> legs and forearms, toes and fingers, penis <i>Mortality:</i> approximately 10%	Calciphylaxis, proximal pattern <i>Synonym:</i> calcific uremic arteriopathy <i>Proximal:</i> trunk, thighs, upper arms <i>Mortality:</i> approximately 50%-70%
Non-ESRD	Martorell HYTILU <i>Synonym:</i> angiodermite nécrotique <i>Distal:</i> laterodorsal leg or Achilles tendon <i>Mortality:</i> approximately 10%	Nonuremic calciphylaxis <i>Synonym:</i> calciphylaxis in normal renal and PTH function or eutrophication in morbid obesity <i>Proximal:</i> trunk, thighs, upper arms <i>Mortality:</i> approximately 50%-70%

Abbreviations: approx, approximately; ESRD, end-stage renal disease; HYTILU, hypertensive ischemic leg ulcer; PTH, parathyroid hormone.

Confusing Martorell HYTILU with pyoderma gangrenosum (PG) can be detrimental to the patient. Necrosectomy (debridement of necrotic tissue), with skin grafting and antibiotic therapy as required, is probably the key to timely and effective treatment of Martorell HYTILU, but an erroneous diagnosis of PG virtually excludes surgical measures from the therapeutic decision.<sup>15</sup>

As noted by Weenig et al,<sup>16</sup> one of the risks of misdiagnosing an inflammatory type of skin ulcer as PG is that the systemic immunosuppression used to treat PG exposes the patients to the risk of sepsis.<sup>16</sup> Therefore, this study also aims to clarify the description of Martorell HYTILU and PG to avoid misdiagnosis and therapeutic decisions.

## METHODS

Medical records of 330 patients with leg ulcers who visited our outpatient or inpatient department between 1999 and 2007 were screened for the diagnosis of Martorell HYTILU (**Figure 1**). We identified 31 patients with both clinically and histologically proven HYTILU, whose files, clinical photodocumentation, and skin biopsy specimens were re-examined. During the same period, 2 patients with calciphylaxis (calcific uremic arteriopathy) and 1 patient with eutrophication in morbid obesity (calciphylaxis with normal renal and parathyroid function) were treated in the department, and their records were also re-evaluated in the present study. The study was submitted to and approved by the local ethics committee.

## DIAGNOSIS

Clinical characteristics that were studied included age, sex, wound location, documentation of pain, diagnosis at the time of referral (specifically PG), medication at the time of referral (specifically antihypertensive or antidiabetic drugs and immunosuppression for supposed PG), and cardiovascular risk factors.

Skin biopsy specimens derived from the wound border were re-examined with a focus on the presence of subcutaneous stenotic arteriosclerosis with or without medial calcification.

Vascular assessment comprised a thorough clinical examination, measurement of the ankle-brachial pressure index (ABPI), segmental oscillography in case of medial calcinosis, and, in the presence of pathologic findings, imaging via fine-needle angiography.

To identify patients with end-stage renal disease (ESRD) or kidney transplant recipients and hence patients with potential calciphylaxis (calcific uremic arteriopathy) or with a primary hyperparathyroidism, the records of all 31 included patients were checked for renal function and parathyroid hormone and calcium phosphate product levels. The latter two were

prospectively determined in the 16 patients who were included in the study between 2005 and 2007.

## TREATMENT

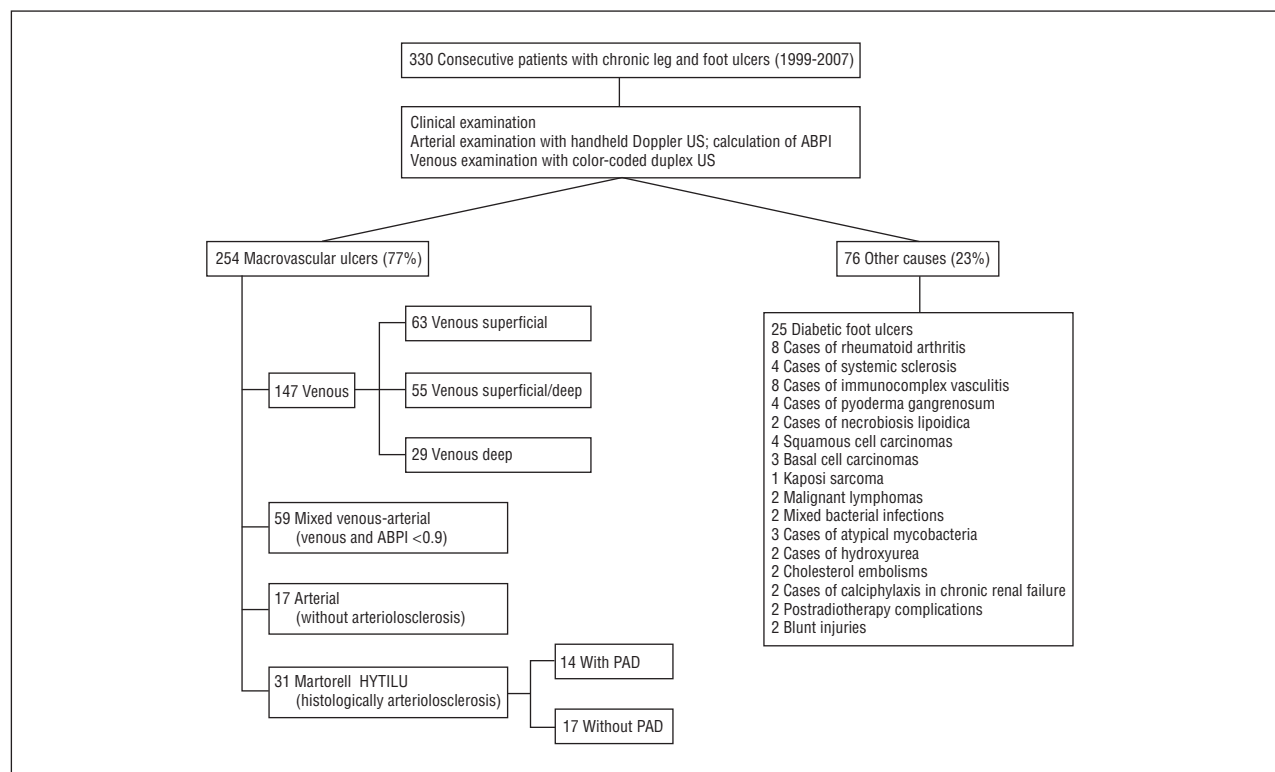
Our standardized treatment protocol for the management of Martorell HYTILU is summarized in **Figure 2**. Basically, the diagnosis is based on the typical history and clinical presentation and confirmed by obtaining a large wedge-shaped biopsy specimen (approximately 5.0 × 0.8 cm, reaching the fascia) starting from healthy skin at the wound border and extending into the necrotic area. Immunosuppression for presumptive PG was stopped and antibiotic treatment initiated as required by the general or local condition. In addition, necrosectomy using adequate—usually tumescent—local anesthesia was undertaken, local negative pressure treatment was started if the wound bed still contained subvital tissue, and split-thickness skin grafting (0.2-mm-thick, meshed graft) was then performed as soon as possible.

## RESULTS

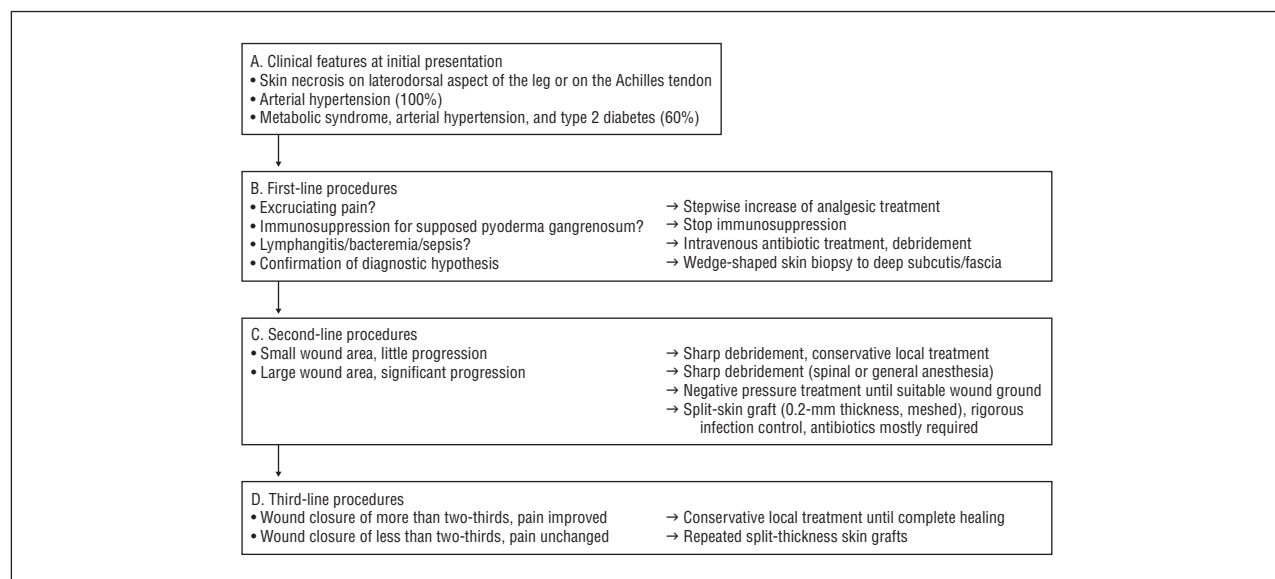
### CLINICAL ASSESSMENT

Of the 31 patients included, 19 (61%) were female, and the mean age of patients was 72 years (range, 61-91 years). The main clinical observation at presentation was skin necrosis with a polycyclic violaceous-black border localized on the laterodorsal part of the leg (**Figure 3**), with a surface area ranging from 2 to 242 cm<sup>2</sup>. Skin necrosis involved the entire subcutis down to the fascia. Sixteen patients (52%) had bilateral lower leg necrosis, and the Achilles tendon was the principal wound location in 4 of the 31 of patients (13%) (**Figure 4** and **Table 2**). Pain was typically strong to excruciating. Seven patients (23%) reported a minor trauma to be the initial trigger, whereas the remaining persons reported a spontaneous onset presenting as a violaceous macule or nodule.

All patients had arterial hypertension and were receiving antihypertensive treatment. It was not possible to collect valid data on the history and duration of hypertension because the majority of patients could not recall the year in which hypertension was diagnosed. However, several patients recalled taking antihypertensive medications for more than 20 years. Of the 31 included patients, 18 (58%) had documented type 2 diabetes mellitus (**Table 2**) and 5 (16%) had a history of cigarette smoking.



**Figure 1.** Study flowchart and etiologic distribution of 330 screened and treated patients. ABPI indicates ankle-brachial pressure index; HYTILU, hypertensive ischemic leg ulcer; PAD, peripheral arterial disease; and US, ultrasonography.



**Figure 2.** Decision model for the management of Martorell hypertensive ischemic leg ulcer.

ing. Of the 25 patients in which lipid levels were recorded, 5 (20%) had elevated serum lipid levels, all of whom were being treated with a statin.

### DIAGNOSIS AT ENTRY

Of the 31 patients, 16 (52%) had a referral letter stating PG as the suspected diagnosis. Of these 16 patients, 9 (56%) were unresponsive to high-dose systemic immunosuppressive drugs, of whom 8 received treatment with

high-dose oral steroids associated with steroid-sparing agents (cyclosporine [n=3], mycophenolate mofetil [n=3], and intravenous cyclophosphamide pulses [n=2]) and 1 received cyclosporine monotherapy.

In another 6 patients (19%), necrotizing cutaneous leukocytoclastic vasculitis was mentioned as the likely diagnosis. Three of these patients were treated with oral steroids, resulting in a total of 12 patients (12 of 31 [39%]) taking immunosuppressive treatment at the time of admission.





**Figure 3.** Clinical features of Martorell hypertensive ischemic leg ulcer (HYTILU) located at the laterodorsal lower leg include skin infarction with central necrosis and progressive inflammatory border. Excruciating pain is typical. The clinical appearance of Martorell HYTILU is often confused with pyoderma gangrenosum or with vasculitis.



**Figure 4.** In approximately 15% of patients, the Achilles tendon can be the next most common location of hypertensive ischemic leg ulcer (HYTILU). When skin necrosis is the only manifestation of Martorell HYTILU, the skin necrosis may be misinterpreted as necrotizing friction blister from footwear.

### HISTOLOGIC CHARACTERISTICS OF SKIN BIOPSY SPECIMENS

Re-examination of the histologic specimens revealed stenotic arteriolosclerosis of the subcutaneous arterioles with an inverse wall to lumen ratio (**Figure 5**). In 22 of 31 patients (71%), medial calcinosis of the subcutaneous arterioles was found to be an additional characteristic feature (**Figure 6B**). Of these 22 patients, 14 (61%) with medial calcinosis of the subcutaneous arterioles were diabetic, compared with 18 of all 31 patients (58%).

**Table 2. Clinical Features of Martorell Hypertensive Ischemic Leg Ulcer**

Clinical Feature	Patients, No. (%) (n=31)
Hypertension (cardiovascular risk factor I)	31 (100)
Diabetes, type 2 diabetes mellitus (cardiovascular risk factor II)	18 (58)
Location: laterodorsal leg	31 (100)
Bilateral occurrence, often separate onset	16 (52)
Histologic feature: arteriolosclerosis	31 (100)
Histologic feature: medial calcinosis	22 (71)
Peripheral arterial disease, confirmed by arteriogram	14 (45)
Initial misdiagnosis as pyoderma gangrenosum	16 (52)
Systemic immunosuppression for assumed pyoderma gangrenosum (n=9) and assumed cutaneous leukocytoclastic vasculitis (n=3)	12 (39)
Fatal outcome due to sepsis (2 of 3 patients were immunosuppressed)	3 (9)
Healed with debridement and split-thickness skin graft (12 of 26 patients had repeated operations)	26 (85)
Healed without surgery	2 (6)

### VASCULAR ASSESSMENT

Fourteen patients (45%) underwent pathologic arterial screening examinations, with medial calcinosis found in 7 (50%). Peripheral arterial disease (>50% stenosis) was confirmed in all 14 patients, and all had lesions that were amenable to percutaneous transluminal angioplasty (Table 2).

Mönckeberg medial calcinosis with incompressible ankle arteries was documented in 11 of 31 cases (35%). Of these 11 patients, 4 (36%) with incompressible ankle arteries had normal oscillography and, therefore, no further investigations, whereas the remaining 7 (64%) underwent angiography.

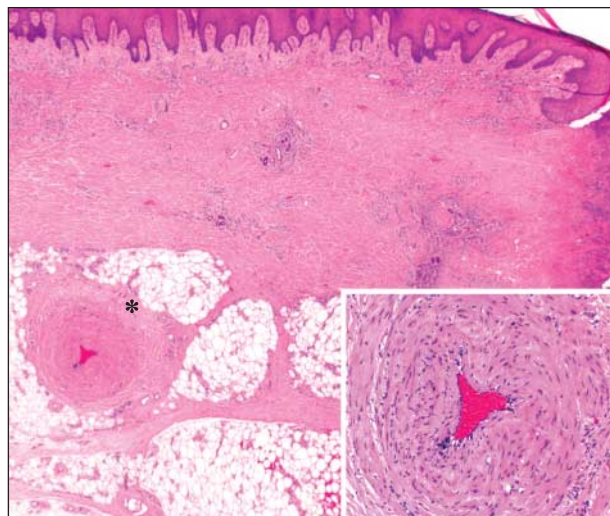
### RENAL FUNCTION, PARATHYROID HORMONE, AND CALCIUM PHOSPHATE PRODUCT

None of the 31 patients with Martorell HYTILU had end-stage chronic renal failure, and none were kidney transplant recipients. Creatinine levels and glomerular filtration rates were normal in 25 of 31 patients (84%) and slightly or moderately impaired (creatinine level, 1.38-1.60 mg/dL [reference range, 0.79-1.19 mg/dL] [to convert to micromoles per liter, multiply by 88.4], and glomerular filtration rate, 34-52 mL/min [reference range, >60 mL/min]) in the remaining 5 (16%).

Among 16 of 31 included patients (52%), parathyroid hormone level was slightly raised (72.1-100.8 pg/mL; reference range, 15-65 pg/mL [to convert to nanograms per liter, multiply by 1.0]) in 6 (38%), of whom 4 had normal renal function and 2 had slightly impaired renal function. In all 16 patients, calcium phosphate product level was normal.

### SURGICAL MANAGEMENT

In only 2 of the 31 patients (6%), wounds were healed with conservative treatment. The remaining patients had refractory wounds, or even progressive skin necrosis. All of these



**Figure 5.** A skin biopsy specimen from the wound edge of a hypertensive ischemic leg ulcer. The asterisk indicates a subcutaneous arteriole with extensive smooth muscle hyperplasia at the price of a narrowed lumen (increased wall to lumen ratio) (hematoxylin-eosin, original magnification  $\times 4$ ).

patients underwent repeated bedside debridement with a disposable ring curette and local anesthesia with EMLA (eutectic mixture of lidocaine and prilocaine) cream, or they underwent sharp necrosectomy in the operating room, usually with tumescent local anesthesia and some required spinal or general anesthesia. Vacuum-assisted negative pressure local wound care was used in 18 patients (58%). Twenty-six patients (85%) received autologous split-thickness skin grafts, of whom 14 (54%) were grafted once; 7 (27%), twice; and 4 (15%), 3 times; and 1 required 6 successive skin grafting procedures.

### OUTCOME

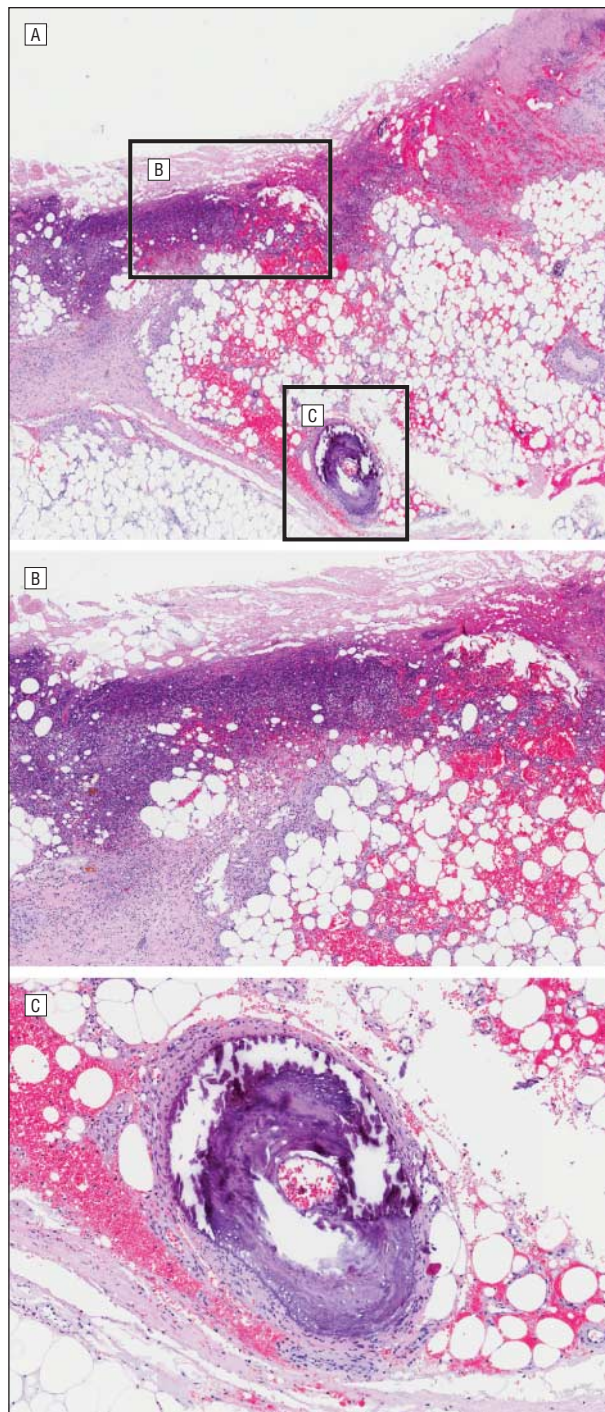
By the end of the study, 28 patients (91%) survived and finished the treatment protocol with completely healed wounds. Three patients (9%), all of whom had extensive skin necrosis and 2 of whom had received immunosuppressive therapy for suppurated PG, died of sepsis during the active phase of disease.

### PAIN MANAGEMENT

All patients reported strong or even excruciating pain at study entry (8-10 on a visual analog scale ranging from 0 to 10). The multistaged medical treatment of pain consisted sequentially of nonsteroidal anti-inflammatory drugs (particularly paracetamol and metamizol), oral or transcutaneous morphine derivatives, tricyclic antidepressive agents, and pregabalin. Patients who did not respond adequately to this regimen within 5 days of onset were referred to the pain control unit of the department of anesthesiology. Skin grafting was by far the single most effective treatment for pain.

### COMMENT

On the basis of our case series and review of the medical literature,<sup>1-14</sup> we suggest grouping the 4 medical conditions with ischemic subcutaneous arteriosclerosis as a



**Figure 6.** A large 5.0  $\times$  0.8-cm spindle-shaped biopsy specimen from healthy-looking skin and skin leading into the wound. Many physicians do not dare to perform such a large biopsy but rather take a punch biopsy from the necrotic wound ground. The figure shows an overview of a cross section of the necrotic border of a Martorell hypertensive ischemic leg ulcer (HYTILU) (A) (hematoxylin-eosin, original magnification  $\times 10$ ). Ironically, when taking a punch biopsy from the wound ground of a Martorell HYTILU, one will find a dense neutrophil infiltrate in a necrotic dermis (B) (hematoxylin-eosin, original magnification  $\times 40$ ). In other words, a superficial wound biopsy can imitate the diagnosis of pyoderma gangrenosum at a histologic level and confirm the erroneous suspicion of pyoderma gangrenosum. A clinician, unaware of the existence of Martorell HYTILU, could perform a superficial wound biopsy and receive a histologic confirmation of pyoderma gangrenosum. If the clinician were to perform a long, narrow, and deep biopsy down to fascia, he or she would find the highly characteristic stenotic arterioles in the subcutis (C) (hematoxylin-eosin, original magnification  $\times 40$ ).



common pathophysiologic feature as follows: (1) Martorell HYTILU<sup>1-7</sup>; (2 and 3) calciphylaxis (calcific uremic arteriolopathy)<sup>8-11</sup> in its distal and more serious proximal pattern; and (4) nonuremic calciphylaxis with normal renal and parathyroid function (eutrophication in morbid obesity)<sup>12-14</sup> (Table 1). This characteristic arteriolar pathologic feature represents the most peripheral type of atherosclerosis and seems to be associated with 2 major cardiovascular risk factors often present in patients with Martorell HYTILU, namely long-standing arterial hypertension (in 100% of cases) and diabetes (frequent).

Martorell HYTILU represents the distal pattern of nonuremic calciphylaxis.<sup>1-7</sup> Clinically, it is defined by a rapidly progressive, extremely painful eschar on the laterodorsal side of the leg or on the Achilles tendon. Hypertension and histologically proven subcutaneous arteriolosclerosis (showing medial calcinosis in 70% of specimens) are mandatory to make the diagnosis. The mortality in our series was 9%, and immunosuppression may contribute to increase the risk of potentially fatal septicemia.

Eutrophication<sup>12</sup> represents the proximal pattern of nonuremic calciphylaxis.<sup>13,14</sup> Clinically, it is defined by extensive, rapidly progressive and extremely painful eschar formation on the trunk and proximal extremities, particularly on the proximal and inner portion of the thighs, on the abdomen, and on the breasts.<sup>12-14</sup> Both macroscopically and microscopically, eutrophication cannot be distinguished from calciphylaxis of the proximal pattern.<sup>9</sup> Case reports of eutrophication describe severe comorbid disease, cancer, and liver cirrhosis.<sup>13,14</sup> However, we hypothesize that hypertension and diabetes, which both are regularly found in the context of metabolic syndrome and morbid obesity, may be the driving forces behind calciphylaxis of nonuremic origin. Eutrophication in morbid obesity has been reported to have a mortality of approximately 40% to 60%,<sup>12-14</sup> which is comparable to the proximal pattern of calciphylaxis.<sup>8,9</sup>

In calciphylaxis, an elevated calcium phosphate product level due to secondary hyperparathyroidism has been proposed to be involved in the pathogenesis.<sup>8-11</sup> There is good clinical evidence that an elevated calcium phosphate product level increases the risk for cardiovascular events.<sup>17-20</sup> By analogy, it would appear probable that it also enhances subcutaneous arteriolosclerosis, but this is not easy to prove. Not all ESRD patients with calciphylaxis exhibit secondary hyperparathyroidism, and parathyroidectomy does not result in clinical improvement in all cases.<sup>9</sup>

The matrix protein GLA (serum protein  $\alpha$ 2-Heremans-Schmid glycoprotein/fetuin A) is an effective vascular and tissue protector against calcification.<sup>21-24</sup> Future studies on the aforementioned 4 arteriolosclerosis entities will hopefully investigate the role of this protein in disease pathogenesis. Matrix GLA requires vitamin K-dependent  $\gamma$ -carboxylation to become active, which would support the impression of several authors that the condition of patients with calciphylaxis may deteriorate when they are placed on warfarin therapy.<sup>11</sup>

Martorell HYTILU is certainly more common than diagnosed and reported in the literature (3 case series in the literature from 1966-1995).<sup>4-6</sup> In our series, 50% of patients with Martorell HYTILU were admitted under the

referral diagnosis of PG and another 20% under the diagnosis of necrotizing vasculitis. In the literature, there are a considerable number of cases that indeed could represent Martorell HYTILU instead of "leg ulcers in calcinosis cutis"<sup>25</sup> or, more commonly, PG.<sup>26-29</sup> Moreover, case series reporting the successful surgical management of PG by skin grafts should probably be revisited taking into consideration Martorell HYTILU.<sup>26-29</sup>

Confusing Martorell HYTILU with entities such as PG or vasculitis can be deleterious,<sup>16</sup> since management of the latter 2 diseases is completely different (**Table 3**). Martorell HYTILU requires anti-infectious treatment and wound surgery, and immunosuppression may expose these patients to an increased risk of septicemia. Martorell HYTILU is an extremely painful eschar that usually occurs on the laterodorsal side of the leg in hypertensive patients aged 60 to 75 years, whereas PG presents as more superficial pustular skin breakdown with a less precise location and 50% of patients have one of the characteristically associated diseases such as inflammatory bowel disease. Histologic proof of subcutaneous arteriolosclerosis (Figure 5 and Figure 6A and B) is warranted before making the diagnosis of Martorell HYTILU. Since the results from superficial wound biopsies ("punch" biopsies) can be totally misleading, special attention should be paid to the quality of the biopsy specimen (long, narrow, and deep elliptical biopsy specimen from healthy-looking skin to necrotic skin) (Figure 6).

The wound border in Martorell HYTILU is strikingly inflammatory, so that the existing confusion with PG is to some extent understandable. As with PG, serological parameters of Martorell HYTILU, such as C-reactive protein level and leukocyte counts, can also be markedly elevated during the active phase of disease progression. Martorell HYTILU is initially an atherosclerotic vascular process, and the observed inflammatory response is secondary to the tissue breakdown resulting from local ischemia. The exact cause and pathomechanism of the inflammatory bursts that can be observed during disease progression in Martorell HYTILU are unknown and should be further investigated in future studies.

Duncan and Faris<sup>30</sup> compared the skin perfusion of patients with Martorell HYTILU to that of patients with peripheral arterial disease and normal controls, using a scintigraphic method measuring the elimination of intradermally injected technetium Tc 99m under standardized external compression. Patients with Martorell HYTILU had reduced skin perfusion pressure comparable to that in peripheral arterial disease, which was caused by the locally increased vascular resistance instead of a reduced arterial inflow.

Primary ("essential") arterial hypertension is mainly the result of increased peripheral vascular resistance, which is essentially regulated via the tonus of arterioles.<sup>31</sup> Long-standing arteriolar vasoconstriction can lead to a fixed increase in vessel wall thickness and an inverse wall to lumen ratio ("athletic" arterioles as described by Hines and Farber and colleagues<sup>2,3</sup>) (Figure 5). The specificity of this finding for the diagnosis of Martorell HYTILU has not been defined. This could be done by a comparative study on cadaveric skin of the laterodorsal leg of a control group of patients.

**Table 3. Martorell HYTILU, Calciphylaxis, Nonuremic Calciphylaxis, and Pyoderma Gangrenosum**

Feature	Martorell HYTILU	Calciphylaxis	Nonuremic Calciphylaxis	Pyoderma Gangrenosum
Hypertension	100% By definition	100%	100%	Possible, not related
Diabetes	60% Frequency in this series	Diabetic nephropathy	Type 2 diabetes very frequent	Possible, not related
Morbid obesity	Frequent	Possible, not related	100% By definition	Possible, not related
Kidney disease	No	100% By definition	No	Rarely, not related
Inflammatory bowel disease or hematoproliferative disease	Rarely, not related	Rarely, not related	Rarely, not related	50%
Histologic feature				
Subcutaneous arteriolosclerosis	100% By definition	100% By definition	100%	No
Dense neutrophilic infiltrates	Yes, caution with a superficial biopsy	Yes, caution with a superficial biopsy	Yes, caution with a superficial biopsy	Yes
Location	Laterodorsal leg, Achilles tendon	Acral, distal and proximal but not head	Proximal skin	Any location
Systemic treatment	Antihypertensive, control of diabetes	Support kidney function, lower phosphate level, discuss sodium thiosulfate	Antihypertensive, control of diabetes, weight loss, discuss sodium thiosulfate	Immunosuppression
Local treatment	Debride necrotic material and split-thickness skin graft	Debride necrotic material and split-thickness skin graft	Debride necrotic material and split-thickness skin graft	Surgery is contraindicated

Abbreviations: HYTILU, hypertensive ischemic leg ulcer; PTH, parathyroid hormone.

Some authors believe that arteriole thrombosis is a decisive criterion for making a diagnosis of ischemic arteriolosclerosis, particularly in calciphylaxis.<sup>7,8</sup> We cannot confirm this hypothesis, since approximately half of the arterioles examined in our specimens were patent. Arteriole thrombosis can occur either primarily or subsequent to tissue breakdown, and the two cannot be distinguished by histopathologic analysis. However, this question could be addressed in future studies using serial sections of the wound border of larger necrosectomy specimens.

The characteristic location of Martorell HYTILU on the laterodorsal side of the leg or the Achilles tendon<sup>4</sup> is not explained to date, but it is most probably related to the anatomy of calf arteries, arterial perforators, and the distribution of subcutaneous arterioles in the leg. Corrosion preparations of amputated limbs of patients with known subcutaneous arteriolosclerosis or postmortem investigations could be helpful in addressing these open questions.

Recent reports promise progress in both conservative and surgical treatment of uremic and nonuremic forms of ischemic arteriolosclerosis. The introduction of the calcimimetic cinacalcet<sup>32</sup> and of the polymeric (and calcium-free) intestinal phosphate binder sevelamer<sup>33</sup> seem to have a beneficial effect on the incidence of macrovascular events in patients with relevant medium-size artery (such as coronary artery) calcification. Cinacalcet has at least been used twice successfully to treat patients with calciphylaxis<sup>11</sup>; however, these promising reports need to be validated in larger series of patients or, ideally, controlled studies. Of even more interest is the intravenous use of sodium thiosulfate for classic calciphylaxis<sup>34</sup> as well as nonuremic forms of calciphylaxis.<sup>35</sup> The beneficial effect of sodium thiosulfate is ascribed to its potential to dissolve

already precipitated calcium salts in the vessels and tissues.<sup>34,35</sup> Empirically, it has been administered 3 times per week intravenously, eg, before dialysis in patients with ESRD. It causes extensive metabolic acidosis and therefore requires specialized monitoring and equipment.

Adequate therapeutic control of hypertension does not appear to be sufficient for the treatment of Martorell HYTILU. All our patients with newly diagnosed Martorell HYTILU were receiving adequate antihypertensive treatment on admission. It seems that the active process of Martorell HYTILU cannot be stopped or reversed with intensified medical antihypertensive treatment alone. Future epidemiologic studies may answer the question as to how well optimal antihypertensive control over many years may prevent the occurrence of Martorell HYTILU.

The incidence of Martorell HYTILU may be on the rise owing to better recognition, an actual increase in incidence, or both. We hypothesize that improved antihypertensive treatment helps to extend a patient's life expectancy and decreases the rate of death due to major cardiovascular complications early in life, specifically myocardial infarction and stroke, which may have contributed to the apparent increase in frequency of Martorell HYTILU. Martorell HYTILU may thus be understood as late "minor" vascular complication of long-standing arterial hypertension in a population that benefits from improved antihypertensive treatment.

Ischemic arteriolosclerosis appears to be a unifying clinicopathological concept for 4 clinical entities that share a common pathophysiologic mechanism, namely (1) distal calciphylaxis (uremic); (2) distal Martorell HYTILU (nonuremic); (3) proximal calciphylaxis (uremic); and (4) eutrophication in morbid obesity or proximal nonuremic calciphylaxis. We suggest that ischemic subcutaneous arteriolosclerosis may be caused by 2 well-established clas-



sic cardiovascular risk factors: long-standing arterial hypertension and diabetes. For disease management, it is of utmost importance that these diseases are not confused with PG or necrotizing vasculitis because their treatment is completely different (namely surgical), and exposing patients with tissue necrosis due to ischemic arteriolosclerosis to systemic immunosuppression may raise the risk of septicemia.

Future studies should address the role of the calcification protective matrix protein GLA, as well as the cytokine pattern during the inflammatory phase of progressive tissue breakdown that characterizes the aforementioned diseases causing ischemic arteriolosclerosis and skin lesions. Furthermore, morphological questions regarding the vascular pathologic mechanisms (eg, the role of calcification, intimal hyperplasia, and thrombosis) and the peculiar location of the skin necroses in Martorell HYTILU should be further studied. Therapeutic studies may help define the value of the nonsurgical approach using sodium thiosulfate compared with the surgical approach using early escharectomy and mesh grafting.

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**Correspondence:** Jürg Hafner, MD, Department of Dermatology, University Hospital of Zurich, Gloriastrasse 31, CH-8091 Zurich, Switzerland (juerg.hafner@usz.ch).

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## REFERENCES

- Martorell F. Las úlceras supramaleolares por arteriolitis de las grandes hipertensas. *Actas (Reun Cientif Cuerpo Facul) Inst Policlinico Barcelona*. 1945;1(1):6-9.
- Hines EA, Farber EM. Ulcer of the leg due to arteriosclerosis and ischemia, occurring in the presence of hypertensive disease (hypertensive-ischemic ulcers): a preliminary report. *Proc Staff Meet Mayo Clin*. 1946;21:337-346.
- Farber EM, Hines EA Jr, Montgomery H, Craig W. The arterioles of the skin in essential hypertension. *J Invest Dermatol*. 1947;9(6):285-298.
- Schnier BR, Sheps SG, Juergens JL. Hypertensive ischemic ulcer: a review of 40 cases. *Am J Cardiol*. 1966;17(4):560-565.
- Lazareth I, Priollet P. Necrotic angiodermatitis: treatment by early cutaneous grafts [in French]. *Ann Dermatol Venerol*. 1995;122(9):575-578.
- Henderson CA, Hight AS, Lane SA, Hall R. Arterial hypertension causing leg ulcers. *Clin Exp Dermatol*. 1995;20(2):107-114.
- Graves JW, Morris JC, Sheps SG. Martorell's hypertensive leg ulcer: case report and concise review of the literature. *J Hum Hypertens*. 2001;15(4):279-283.
- Hafner J, Keusch G, Wahl C, et al. Uremic small-artery disease with medial calcification and intimal hyperplasia (so-called calciphylaxis): a complication of chronic renal failure and benefit from parathyroidectomy. *J Am Acad Dermatol*. 1995;33(6):954-962.
- Hafner J, Keusch G, Wahl C, Burg G. Calciphylaxis: a syndrome of skin necrosis and acral gangrene in chronic renal failure. *Vasa*. 1998;27(3):137-143.
- Llach F. Calcific uremic arteriopathy (calciphylaxis): an evolving entity? *Am J Kidney Dis*. 1998;32(3):514-518.
- Weenig RH, Sewell LD, Davis MD, McCarthy JT, Pittelkow MR. Calciphylaxis: natural history, risk factor analysis, and outcome. *J Am Acad Dermatol*. 2007;56(4):569-579.
- Ramsey-Stewart G. Eutrophication: spontaneous progressive dermatoliponecrosis: a fatal complication of gross morbid obesity. *Obes Surg*. 1992;2(3):263-264.
- Kalajian AH, Malhotra PS, Callen JP, Parker LP. Calciphylaxis with normal renal and parathyroid function: not as rare as previously believed. *Arch Dermatol*. 2009;145(4):451-458.
- Nigwekar SU, Wolf M, Sterns RH, Hix JK. Calciphylaxis from nonuremic causes: a systematic review. *Clin J Am Soc Nephrol*. 2008;3(4):1139-1143.
- Conrad C, Trüeb RM. Pyoderma gangrenosum. *J Dtsch Dermatol Ges*. 2005;3(5):334-342.
- Weenig RH, Davis MD, Dahl PR, Su WP. Skin ulcers misdiagnosed as pyoderma gangrenosum. *N Engl J Med*. 2002;347(18):1412-1418.
- Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis*. 1998;31(4):607-617.
- Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. *Hypertension*. 2001;38(4):938-942.
- Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. *J Am Soc Nephrol*. 2004;15(8):2208-2218.
- Block GA, Raggi P, Bellasi A, Kooienga L, Spiegel DM. Mortality effect of coronary calcification and phosphate binder choice in incident hemodialysis patients. *Kidney Int*. 2007;71(5):438-441.
- Schäfer C, Heiss A, Schwarz A, et al. The serum protein alpha 2-Heremans-Schmid glycoprotein/fetuin-A is a systemically acting inhibitor of ectopic calcification. *J Clin Invest*. 2003;112(3):357-366.
- Heiss A, DuChesne A, Denecke B, et al. Structural basis of calcification inhibition by alpha 2-HS glycoprotein/fetuin-A: formation of colloidal calciprotein particles. *J Biol Chem*. 2003;278(15):13333-13341.
- Luo G, Ducy P, McKee MD, et al. Spontaneous calcification of arteries and cartilage in mice lacking matrix GLA protein. *Nature*. 1997;386(6620):78-81.
- Wallin R, Cain D, Sane DC. Matrix Gla protein synthesis and gamma-carboxylation in the aortic vessel wall and proliferating vascular smooth muscle cells—a cell system which resembles the system in bone cells. *Thromb Haemost*. 1999;82(6):1764-1767.
- Zutt M, Hallermann C, Gutgesell C, Bertsch HP, Neumann C. Idiopathische Calcinosis cutis mit ausgedehnten Unterschenkelulzera. *Phlebologie*. 2002;31(2):50-55.
- Davis JC, Landeen JM, Levine RA. Pyoderma gangrenosum: skin grafting after preparation with hyperbaric oxygen. *Plast Reconstr Surg*. 1987;79(2):200-207.
- Cliff S, Holden CA, Thomas PR, Marsden RA, Harland CC. Split skin grafts in the treatment of pyoderma gangrenosum: a report of four cases. *Dermatol Surg*. 1999;25(4):299-302.
- Kaddoura IL, Amm C. A rationale for adjuvant surgical intervention in pyoderma gangrenosum. *Ann Plast Surg*. 2001;46(1):23-28.
- Gherzi MM, Ricotti C, Nousari CH, Newman MI. Negative pressure dressing in the management of pyoderma gangrenosum ulcer. *Arch Dermatol*. 2007;143(10):1249-1251.
- Duncan HJ, Faris IB. Martorell's hypertensive ischemic leg ulcers are secondary to an increase in the local vascular resistance. *J Vasc Surg*. 1985;2(4):581-584.
- Feihl F, Liaudet L, Waeber B, Levy BI. Hypertension: a disease of the microcirculation? *Hypertension*. 2006;48(6):1012-1017.
- Block GA, Martin KJ, de Francisco ALM, et al. Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med*. 2004;350(15):1516-1525.
- Suki WN, Zabaneh R, Cangiano JL, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int*. 2007;72(9):1130-1137.
- Cicone JS, Petronis JB, Embert CD, Spector DA. Successful treatment of calciphylaxis with intravenous sodium thiosulfate. *Am J Kidney Dis*. 2004;43(6):1104-1108.
- Hackett BC, McAleer MA, Sheehan G, Powell FC, O'Donnell BF. Calciphylaxis in a patient with normal renal function: response to treatment with sodium thiosulfate. *Clin Exp Dermatol*. 2009;34(1):39-42.